Monika Mehta et al., Pharm Anal Acta 2018, Volume 9
DOI: 10.4172/2153-2435-C1-033

Themis-associated phosphatase activity controls signaling in T cell development

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Themis (Thymocyte expressed molecule involved in selection) has been shown to be important for T cell selection, for setting the threshold for positive versus negative selection. Themis interacts with the protein tyrosine phosphatase Shp1, a negative regulator of the T cell receptor-signaling cascade. However, how Themis regulates Shp1 is still not clear. Using a very sensitive phosphatase assay on *ex vivo* thymocytes, we have found that Themis enhances Shp1 phosphatase activity. The regulation of Shp1 activity by Themis is found in thymocytes, but not in peripheral T cells, possibly due to differences in the relative abundance of the two proteins, as a larger proportion of Shp1 is associated with Themis in thymocytes than it is in peripheral T cells. Themis has associated phosphatase activity, due to its constitutive interaction with Shp1, which is modulated by different affinity ligands in thymocytes. These findings demonstrate unequivocally that Themis positively regulates Shp1 phosphatase activity in TCR-mediated signaling in developing thymocytes. In order to further validate these findings, Themis-Shp1 double knockout mice are made and interestingly, it is found that these mice have similar thymic development defect as that of Themis KO, however, in periphery; there was a partial rescue phenotype, which suggested that Themis does play different roles in thymus versus periphery. Understanding the molecular mechanism behind the regulation of Shp1 activity by Themis and its effects on the signaling cascades is clearly important in understanding how the TCR repertoire is formed, so that T cells are able to respond to foreign antigens but not to be autoimmune at the same time. As Shp1 is expressed in many cell types, but Themis is T cell-specific, understanding how Themis regulates signaling through Shp1 in mature T cells could in principle provide a means to modulate the immune response and suggest ways to alter the Shp1 activity in non-T cell types.

Biography

Monika Mehta is a recent graduate from Professor Nicholas Gascoigne's lab at NUS. During her Doctorate studies, she worked on a new protein called Themis and looked at the mechanism of its regulation of T cell development via Shp1. She independently developed an assay to study the phosphatase activity associated with precipitated proteins. She also received Medical top up Scholarship from Yong Loo Lin School of Medicine for being in the top two international PhD students. She also represented Singapore in "Lindau Nobel Laureate Meetings" in 2014, a very prestigious meeting led by 35 Nobel laureates from medicine held in Germany. She attained Masters in Biotechnology from University of Hyderabad, India, with three Gold medals for being the top student among all the departments in the university.

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